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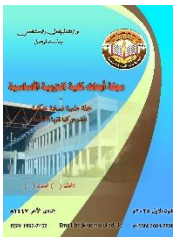

Synthesis and Characterization of Some New Heterocyclic Compounds (Thiazolidine, Tetrazole And Azetidinone) from Schiff Bases Contain 1,4-Dihydropyridine

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Abstract

This study involves the synthesis of new Schiff bases and heterocyclic compounds beginning from 3,5-diacetyl-2,6-dimethyl-1,4-dihyropyridine as the starting material. To Characterize the prepared compounds, uses the physical properties such as melting point and color, additionally the spectroscopic techniques FT-IR, ^{1}H-NMR, ^{13}C-NMR, TLC. Given the importance, it is used in many fields such as drugs and pharmaceutical industry and have biological actions including antifungal, antiviral, antibiotics and anticancer.

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تحضير وتشخيص بعض المركبات الحلقية غير المتجانسة الجديدة (ثيازوليدين، وتترازول، وأزيتيدينون) من قواعد شيف التي تحتوي على 4،1-ثنائي هيدروبيريدين

ناريمان حميد ابراهيم **منيرة يوسف رؤوف**

جامعة الموصل، كلية العلوم، قسم الكيمياء، الموصل، العراق.

المستخلص

تتضمن هذه الدراسة تحضير قواعد شيف جديدة ومركبات حلقية غير متجانسة ابتداءآ من 5،3-ثنائي أسيتيل-6،2-ثنائي ميثيل-4،1-ثنائي هيدروبيريدين كمادة أولية. ولتشخيص المركبات المُحضّرة، استخدمت الخصائص الفيزيائية كدرجة الانصهار واللون، بالإضافة الى تقنيات التحليل الطيفي مثل الاشعة تحت الحمراء والرنين النووي المغناطيسي وكروموتوغرافيا الطبقة الرقيقة ونظرًا لأهميتها، تُستخدم هذه المركبات في العديد من المجالات كالصناعات الدوائية والصيدلانية، ولها تأثيرات بيولوجية تشمل مضادات الفطريات والفيروسات والمضادات الحيوية ومضادات السرطان.

الكلمات المفتاحية: قواعد شف ، ومركبات حلقية غير متجانسة، ثيازوليدين، وتترازول، وأزيتيدينون.

1. Introduction

Chemists have consistently faced distinct challenges in heterocyclic chemistry because of its vast knowledge base and variety (Peerzada et al., 2021). Despite this, heterocyclic chemistry and synthesis methods continue to be crucial in modern medicinal and pharmaceutical research (González-Andrés et al., 2021). Nitrogen-based heterocyclic compounds are recognized as a dominant group of chemicals among biologically active substances, natural compounds, and those commonly applied in medicinal chemistry(Nilkanth et al., 2020)(Marín-Ocampo et al., 2019) . In a similar vein, heterocyclic compounds containing sulfur form a large segment of FDA-approved pharmaceuticals and are known for their therapeutic potential(Qadir et al., 2022).

Heterocyclic compounds have diverse applications, with their primary use in pharmaceuticals, agrochemicals, and veterinary products. They are also used as sanitizers, developers, corrosion inhibitors, copolymers, and dyes(Arora et al., 2012).

These chemicals have been found to possess biological properties as antifungal (Al-Mulla, 2017), anti-inflammatory (Sandhu et al., 2023), antibacterial (Kareem et al., 2024), anticonvulsant, antiviral (Jawad et al., 2012), antioxidant (Kabir & Uzzaman, 2022) , anticancer activity (Kidwai et al., 2002).

In our research, we aim to synthesize a Schiff base from 1,4-dihydropyridine and then cyclize it with thioglycolic acid, sodium azide, and chloroacetyl chloride to create derivatives of thiazolidine, tetrazole, and azetidinone rings. We will also characterize the resulting products using a variety of techniques.

2. Material and methods

2.1 Materials & Instruments

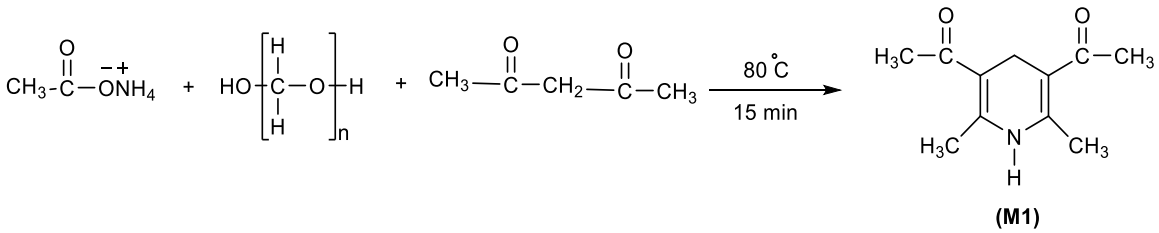
All chemicals used were of analytical grade and were supplied by Aldrich, Fluka, BDH, CDH, Scharlau, or Thomas Baker.

Used spectroscopic methods, including FT-IR, ^{1}H NMR, and ^{13}C NMR additionally, their physical properties, such as melting points and TLC to identification the prepared compounds.

2.2 Synthesis of Prepared Compounds

A. Synthesis of 3,5-diacetyl-2,6-dimethyl-1,4-dihyropyridine (M1)

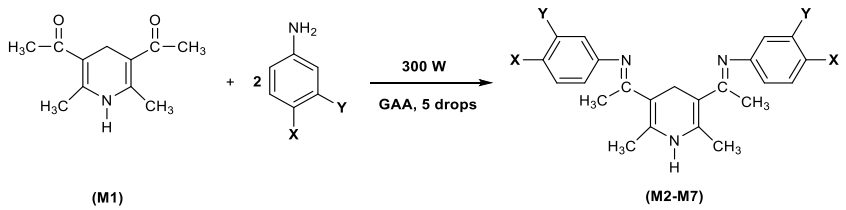
The starting material 3,5-diacetyl-2,6-dimethyl-1,4-dihyropyridine (M1) was prepared by the Hantzsch reaction as in the source (Yahya & Roof, 2022) as shown equation(1).



Equation 1: Synthesis of started material (M1)

B. Synthesis of Schiff Base Compounds (M2-M7)

Schiff base compounds were prepared by reflux and microwave methods according to the following source (Shntaif & Rashid, 2016) and (Habeeb & Sheat, 2023) see equation (2).



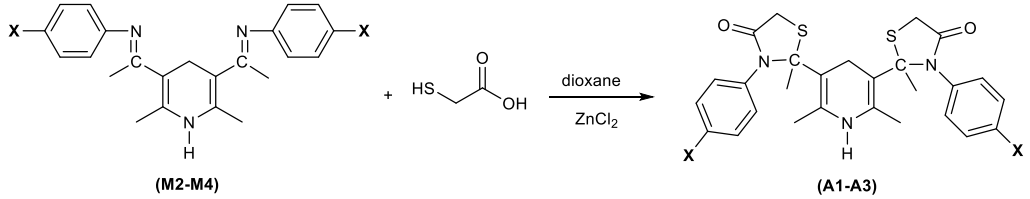
Comp. No.	X	Y
M2	NO_2	H
M3	COOH	H
M4	Br	H
M5	H	NO_2
M6	Cl	H
M7	CH_3	Cl

Equation 2: Synthesis of Schiff base compounds (M2-M7)

C. Synthesis of Thiazolidine Derivatives (A1-A3)

The following mixture was refluxed with stirring for 24 hours: 0.001 mol of Schiff base compounds (M2-M4), 0.002 mol (0.18 g) of thioglycolic acid, and 0.002 mol (0.27 g) of zinc chloride (II) in 25 ml of dioxane. The resulting solid

product was then filtered, dried, and recrystallized with ethanol as shown in Equation (3) (Fayyadh & Al-rawi, 2023) and Table (1) show the physical properties of prepared thiazolidine derivatives.

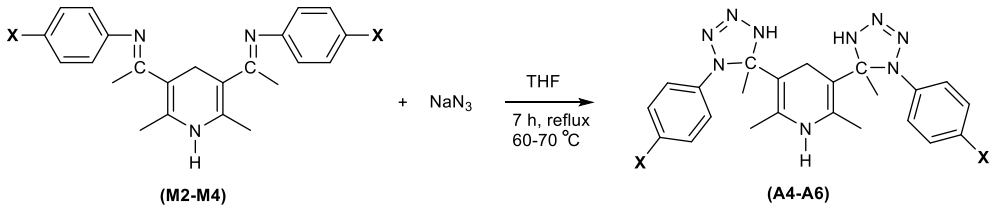


Equation 3: Chemical reaction of synthesis of Thiazolidine derivatives.

D. Synthesis of Tetrazole Derivatives (A4-A6)

Schiff base compounds (M2-M4) (0.001 mol) were dissolved in 25 ml of tetrahydrofuran (THF). After heating the solution in a water bath at 60-70°C for 7 The hours, sodium azide (0.002 mol) was added. This resulted in the immediate formation of a crystalline precipitate, which was then recrystallized from methanol.

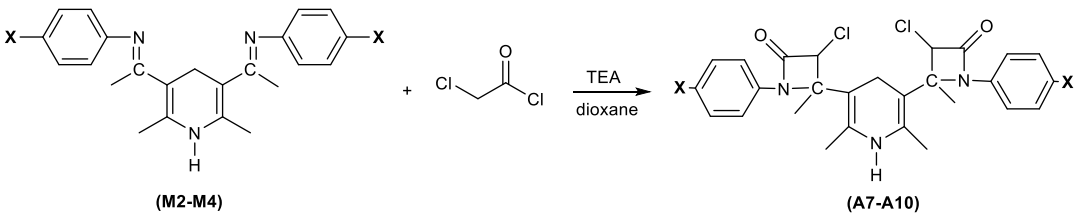
The physical properties of the synthesized compound are listed in Table (1) and the chemical reaction represent in the Equation (4) (Hassan & Omar, 2023).



Equation 4: Chemical reaction of synthesis of Tetrazole derivatives.

E. Synthesis of Azetidinone Derivatives (A7-A10)

A solution was prepared by dissolving 0.005 mol of Schiff base compounds (M2-M5) and 0.01 mol of triethylamine (TEA) in 30 ml of 1,4-dioxane. To this mixture, 0.01 mol of chloroacetyl chloride was added, followed by shaking and cooling for 20 minutes. The resulting product was concentrated, cooled, filtered, dried, and then recrystallized using ethanol. The physical features of the compounds are shown in Table (1) and the general chemical reaction of the prepared compounds corresponding to Equation (5) (Muhammed, 2023).



Equation 5: The general reaction of synthesis the Azetidinone Derivatives.

Table 1: The Physical properties of prepared compounds.

Comp. No.	Color	M.p ºC	Yield %
M2	Brown	126-128	81
M3	Deep Brown	137-139	75
M4	Green	197-199	78
M5	Brown	115-117	80
M6	Deep Brown	164-166	60
M7	Light Brown	143-145	67
A1	Off White	> 300	75
A2	Black	247-249	69
A3	Off White	> 300	84
A4	Brown	>300	63
A5	Off White	297-299	60
A6	White	>300	75
A7	Brown	253-254	91
A8	Off White	231-232	96
A9	Light Brown	248-289	92
A10	White	260-261	90

3. Results and Discussion

The compound (3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine) (M1) was synthesized via a three-component reaction using paraformaldehyde, acetylacetone, and ammonium acetate as the starting materials. Following this, Schiff base compounds (M2-M7) were obtained by reacting (M1) as the ketone with various substituted anilines, including 4-nitroaniline, 4-aminobenzoic acid,

4-bromoaniline, 3-nitroaniline, 4-chloroaniline, and 3-chloro-4-methylaniline, using both traditional and green methods. Finally, these compounds were cyclized with reagents like thioglycolic acid, sodium azide, and chloroacetyl chloride, resulting in the formation of heterocyclic compounds such as thiazolidine, tetrazole, and azetidinone derivatives (A1-A10).
The synthesized compounds were characterized through spectroscopic methods, including FTIR, ^{1}H-NMR, ^{13}C-NMR, and TLC, in addition to their physical properties. Table 1 presents a detailed summary of these compounds' physical characteristics, such as melting points, color, metal content, and other pertinent attributes. This information enhances the understanding of the properties of the synthesized compounds.

3,5-diacetyl-2,6-dimethyl-1,4-dihyropyridine DHP (M1)
The compound (M1) was efficiently synthesized using the traditional Hantzsch method by heating a mixture of paraformaldehyde, acetylacetone, and ammonium acetate in water. The reaction produced a yield of 52%, and the compound exhibited a melting point of 215-217°C, compared to the published melting point of 215-217°C (Abdel-Mohsen et al., 2012).
The synthesized 3,5-diacetyl-2,6-dimethyl-1,4-dihydropyridine was characterized based on its spectral data from FT-IR and its melting point, which was compared to the published value. The FT-IR spectrum showed key bands at 3380 cm^{-1}, 1668 cm^{-1}, and 1642 cm^{-1}, corresponding to the stretching vibrations of the N-H, C=O, and C=C groups, respectively.

Synthesis of Schiff Base Compounds (M2-M7)
The new Schiff bases were prepared using two techniques: a green method employing microwave irradiation at 300W and a conventional method involving reflux. (Farhan et al., 2022) & (Shntaif & Rashid, 2016)**.**

The reaction pathway was confirmed by assessing specific physical properties, such as the melting points and comparing them to those of the reactants, along with noting color changes in the final compounds. The structures of the synthesized compounds were determined using physical properties, such as the melting points and comparing them to those of the reactants and color, addition, spectroscopic techniques like FT-IR, ^{1}H-NMR, and ^{13}C-NMR. Figures (1-3) show the disappearance of the absorption peak at 3350-3480 cm^{-1}, corresponding to the amino group $\upsilon(NH_2)$, and the peak at 1668 cm^{-1}, associated with the carbonyl group υ(C=O) from the starting material. Simultaneously, a new

absorption peak emerged in the range of 1626-1672 cm^{-1}, attributed to υ(C=N), with additional bands presented in Table (2).

Table 2: FT-IR bands of the prepared Schiff base compounds (M2-M7) in cm^{-1}.

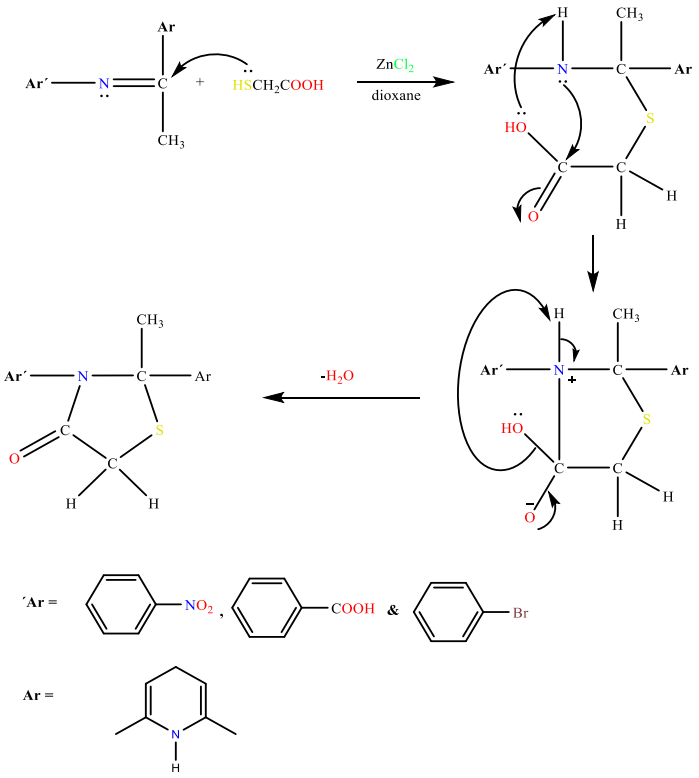
Comp. No.	υ N-H	υ C-H arom.	υ C-H aliph.	υ C=N	υ C=C Conj.	υ C-C arom.	Others
M2	3355	3108	2910, 2842	1628	1585	1532	1504 asymm. N-O 1293 symm. N-O
M3	3353	3226	2965, 2820	1626	1595	1521	3461 O-H,1662 C=O,1285 C-O
M4	3381	3036	2909, 2877	1686	1642	1588	618 C-Br
M5	3301	3005	2926, 2848	1677	1657	1575	1478 asymm. N-O 1216 symm. N-O
M6	3381	3192	2971, 2877	1672	1672	1581	741 C-Cl
M7	3254	3105	2923, 2847	1645	1599	1535	824 C-Cl

The ^{1}H-NMR spectra of the Schiff base compound (M2-M7), depicted in Figures (4-6), reveal a singlet signal between 8.52-9.85 ppm, corresponding to the single proton of the (N-H) group. Multiple peaks appearing between 6.57-8.30 ppm are likely attributed to the eight aromatic protons. Additionally, a signal in the range of 3.33-4.07 ppm is assigned to two protons from the pyridine ring, while peaks around 2.01-2.27 and 2.62-3.37 ppm correspond to twelve protons from the methyl groups, with the first set attached to the imine and the second set to the pyridine ring.

The ^{13}C-NMR spectra, recorded at 100 MHz using DMSO as the solvent, are listed in Table (6). A signal at 40 ppm, corresponding to the DMSO solvent, is present in all spectra, as shown in Figures (7 & 8).

Synthesis of Thiazolidine Derivatives (A1-A3)

One equivalent mole of Schiff base compounds (M2-M4) was cycled with two equivalent moles of thioglycolic acid and two equivalent moles of zinc chloride in dioxane under reflux for ten hours to create the compounds (A1-A3), (Abid & Ahmed, 2018). The proposed mechanism of synthesis thiazolidine derivatives, as illustrated bellow:



The structure of the thiazolidine derivatives was determined using spectroscopic methods, including FTIR, ^{1}H-NMR, and ^{13}C-NMR. The FTIR spectra show absorption bands, such as the υ(N-H) vibration of the DHP group in the thiazolidine target, which appeared in the range of 3347-3384 cm^{-1}. The bands corresponding to the lactam (C=O) group were observed between 1644-1697 cm^{-1}, while the crucial bands for the (C-S-C) group, indicative of the cyclization of thioglycolic acid with Schiff bases, appeared in the range of 753-782 cm^{-1}. These findings are shown in Figure (9) and Table (3).

Table 3: FT-IR bands of thiazolidine derivatives (A1-A3) cm^{-1}

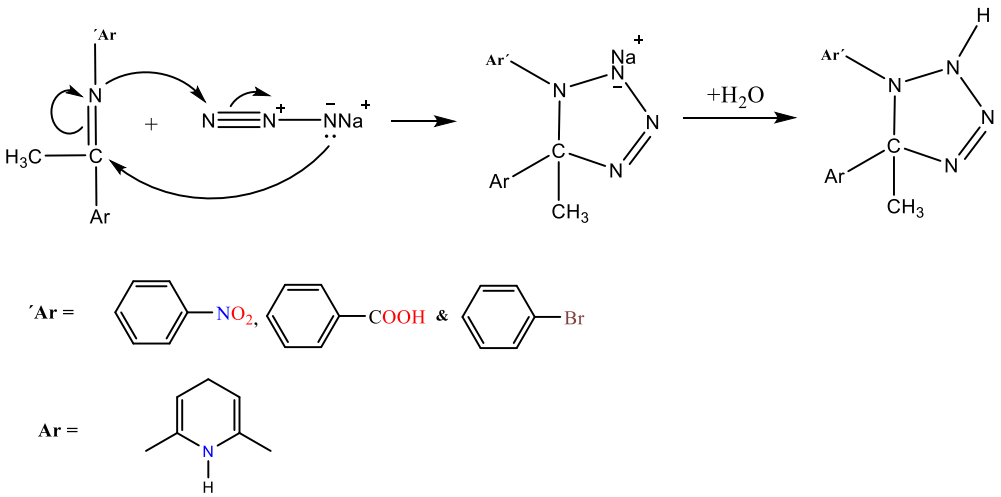
Comp. No.	υN-H	υC-H arom.	υC-H aliph.	υC=O lactam	υC=C	υC-C arom.	υC-S-C	Others
A1	3384	3010	2970, 2890	1644	1613	1534	753	3552 OH, 1662 C=O
A2	3347	3023	2971. 2891	1656	1580	1557	781	1462 N-O asymm. 1315 N-O symm.
A3	3358	3115	2920, 2884	1697	1584	1556	782	569 C-Br

The ^{1}H-NMR spectrum of compound (A3), recorded at 400 MHz in DMSO, features a singlet signal at 8.28 ppm, corresponding to the proton of the N-H group. Additionally, multiple peaks in the range of 8.00-8.07 ppm are attributed to the eight protons of the aromatic ring. A singlet signal for the four protons of the thiazolidine ring is observed at 4.19 ppm, while the protons of the pyridine ring appear at 3.27 ppm. Singlet peaks around 0.99 and 2.40 ppm are associated with the methyl groups, as illustrated in Figure (10).

The ^{13}C-NMR spectrum of compound (A3) displays the following signals: 199.78 ppm for the C=O group, 167.12-123.72 ppm for the aromatic carbons, 62.30 ppm for the (N-C-S) group, and 29.09-18.08 ppm for the CH_2 and CH_3 groups, as shown in figures (11) and in table (6).

Synthesis of Tetrazole Derivatives (A4-A6)

One equivalent mole of Schiff base compounds (M2-M4) was reacted with two equivalent moles of sodium azide in tetrahydrofuran solvent under reflux conditions for ten hours to synthesize the compounds (A4-A6). (Hassan & Omar, 2023). The proposed mechanism of synthesis tetrazole derivatives, as illustrated bellow:



tetrazole compounds were identified using spectral instruments such as FTIR, ^{1}H-NMR and ^{13}C-NMR, FTIR spectra of the compounds (A4-A6), This provides strong evidence that the reactions occurred successfully, as indicated by the disappearance of the strong band at 1628 cm^{-1}, which corresponds to the stretching vibration of the (C=N) imine group. In its place, a strong band appears at lower frequencies in the range of 1384 to 1417 cm^{-1}, attributed to the

stretching vibration of azo groups (N=N). Additionally, the spectrum shows a medium band spanning from 1237 cm^{-1} to 1265 cm^{-1}, corresponding to the vibration of the (N-N) bond. Figure (12) and table (4) present the FT-IR spectrum of compound (A5).

Table 4: FT-IR bands of tetrazole derivatives (A4-A6) cm^{-1}

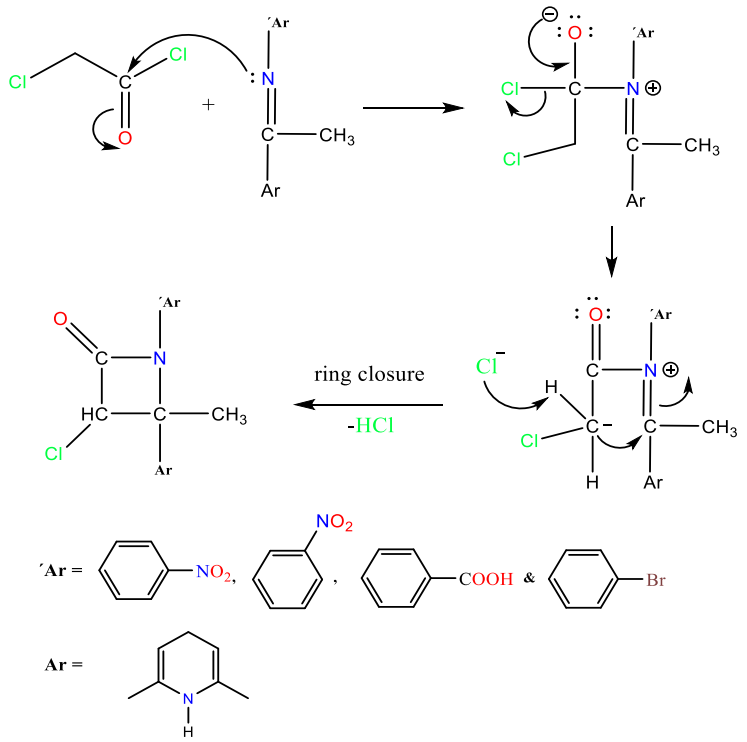
Comp. No.	υN-H	υC-H arom.	υC-H aliph.	υC=C	υC-C arom.	υN=N	υN-N	Others
A4	3307	3101	2929, 2857	1602	1526	1384	1265	3424 OH, 1668 C=O
A5	3321	3013	2995, 2874	1592	1437	1390	1246	1509 N-O asymm. 1376 N-O symm.
A6	3317	3095	2907, 2891	1577	1440	1417	1237	627 C-Br

The ^{1}H-NMR spectrum of compound (A4) displays a singlet signal at 10.69 ppm, which corresponds to the protons of the COOH group, and a singlet peak at 10.38 ppm associated with the protons of the (N-H) group. Additionally, multiple peaks in the range of 7.91 to 8.29 ppm are attributed to aromatic protons, as shown in Figure (13). A singlet peak at 3.96 ppm is observed, relating to the protons of the pyridine group, while the peak at 1.69 ppm corresponds to the N-H protons of the tetrazole ring. Furthermore, singlet signals ranging from 2.49 to 2.98 ppm are assigned to the methyl protons.

The ^{13}C-NMR spectrum of the compound (A4) exhibits the following signals (179.87) ppm for C=O, (149.32-119.80) ppm for aromatic, (129.12,117.23) ppm for pyridine, (95.24) for tetrazole ring, (30.45-18.36) for CH_2 and CH_3 groups, are presented in Table (6).

Synthesis of Azetidinone Derivatives (A7-A10)

This compounds synthesis from react one equivalent mole of Schiff base (M2-M5) with two equivalent moles of chloroacetyl chloride in dioxane as solvent by reflux method. The proposed mechanism of synthesis azetidinone derivatives, as illustrated bellow:



The FTIR spectrum shows a band corresponding to the υ(N-H) vibration of the DHP in the azetidinone target, appearing in the range of 3354-3386 cm^{-1}. The bands associated with the (C=O) lactam group are observed between 1634 and 1729 cm^{-1}, while the key bands corresponding to the aliphatic (C-H) group are found in the ranges of 2944-2979 cm^{-1} and 2877-2883 cm^{-1}. Additionally, there are other vibration bands between 2359 and 2622 cm^{-1}, likely related to the solvent (1,4-dioxane) used in the reaction, as shown in Figure 14 and Table 5.

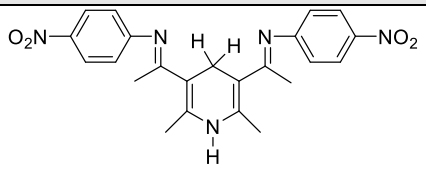
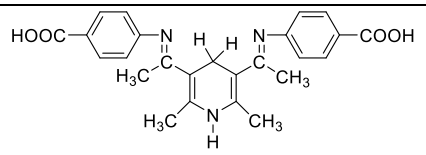
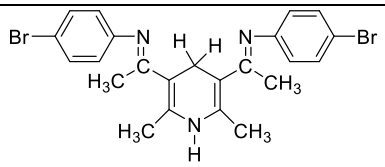
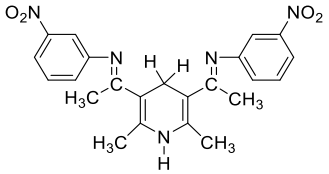
Table 5: FT-IR bands of azetidinone derivatives (A7-A10) cm^{-1}

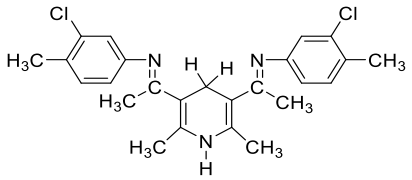
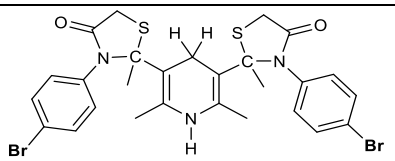
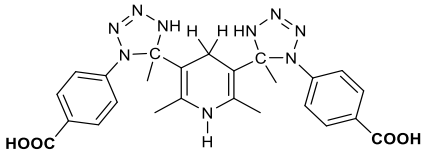
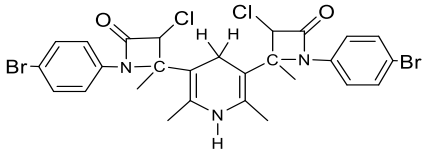
Comp. No.	υN-H	υC-H arom.	υC-H aliph.	υC=O lactam	υC=C	υC-C arom.	Others
A7	3375	3100	2979, 2883	1634	1603	1538	3438 OH, 1699 C=O
A8	3354	3017	2944, 2877	1658	1624	1568	1475 N-O asymm. 1365 N-O symm.
A9	3367	3035	2946, 2883	1691	1629	1588	567 C-Br
A10	3386	3020	2946, 2882	1729	1620	1533	1475 N-O asymm. 1365 N-O symm.

The ^{1}H-NMR spectrum of compound (A9) shows a singlet signal at 8.80 ppm, attributed to the proton of the (N-H) group. The doublet-doublet peaks observed in the range of 7.28 to 7.47 ppm are related to the aromatic protons. A singlet peak at 4.28 ppm corresponds to the two protons of the azetidinone ring, while a singlet at 3.37 ppm is assigned to the protons of the pyridine group. Additionally, signals in the range of 2.68 and 2.75 ppm are associated with the methyl protons. Another signal observed at 3.89 ppm may be attributed to the reaction solvent, dioxane, see Figure (15).

The ^{13}C-NMR spectrum of the compound (A9) observes the following signals (199.05) ppm for C=O, (171.64,168.41and140.65) ppm for aromatic, (157.24,130.97) ppm for pyridine ring, (72.23) ppm for C-Cl, (62.64) ppm for azetidinone ring, (45.05-21.85) ppm for CH_2 and CH_3 as shown table (6) and figure (16).

Table 6: ^{13}C-NMR data of the prepared compounds

Comp. No.	Comp. Structure	^{13}C-NMR (100 MHz, DMSO) ppm
M2		C_{imine} = 159.36, $C_{arom.}$ = (156.38-127.08), $C_{pyridine}$ =(113.04 & 108.30), C_{CH2} = 30.76, $C_{CH3\text{-}pyridine}$ = 24.79, $C_{CH3\text{-}imine}$ = 19.37.
M3		$C_{carbonyl}$ = 200.66, C_{imine} =168, $C_{arom.}$ = (1159.11-131.66), $C_{pyridine}$ = (117.40 & 112.90), C_{CH2} = 33.79, $C_{CH3\text{-}pyridine}$ = 29.99, $C_{CH3\text{-}imine}$ = 24.74.
M4		C_{imine} = 196.34, $C_{arom.}$ = (158.38-130.96), $C_{pyridine}$ =(129.52 & 107.29), C_{CH2} = 29.77, $C_{CH3\text{-}pyridine}$ = 23.97, $C_{CH3\text{-}imine}$ = 18.36.
M5		C_{imine} = 196.92, $C_{arom.}$ = (158.95-120.19), $C_{pyridine}$ = (109.99 & 107.88), C_{CH2} = 30.38, $C_{CH3\text{-}pyridine}$ = 26.65, $C_{CH3\text{-}imine}$ = 18.95.

M7		C_{imine} = 168.50, $C_{arom.}$ = (137.23-130.08), $C_{pyridine}$ = (119.32 & 118.01), C_{CH2} = 72.86, $C_{CH3\text{-}pyridine}$ = 69.88, $C_{CH3\text{-}imine}$ = 59.82, $C_{CH3\text{-}ph}$ =18.73.
A3		$C_{C=O}$= 199.78, $C_{arom.}$= (167.12-123.72), $C_{pyridine}$= (129.46 & 94.92), $C_{N\text{-}C\text{-}S}$= (62.30), $C_{Thiazolidine\ ring}$= 55.57, C_{CH2}= 23.82, C_{CH3}= (29.09 & 18.08)
A4		$C_{C=O}$ = 179.87, $C_{arom.}$ = (149.32,136.66,122.85 & 119.8), $C_{pyridine}$= (129.12,117.23), $C_{tetrazole\ ring}$= (95.24), C_{CH3}= (30.45 & 26.72), C_{CH2}= 18.36.
A9		$C_{C=O}$ = 199.05, $C_{arom.}$= (171.69,168.41 & 140.65), $C_{pyridine}$= (157.24 & 130.97), $C_{C\text{-}Cl}$= 72.23, $C_{azetidinone\ ring}$ = 62.64, C_{CH2}= 29.56, C_{CH3}= (45.05 & 21.85).

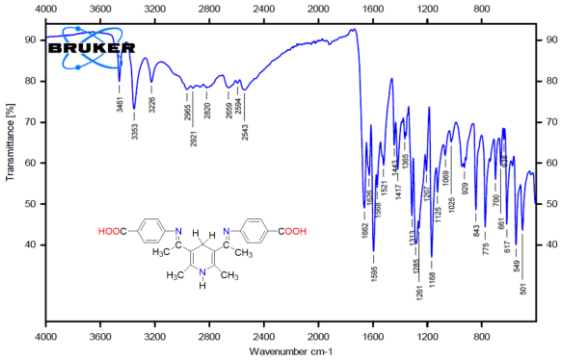


Figure 1: FT-IR of compound (M3)

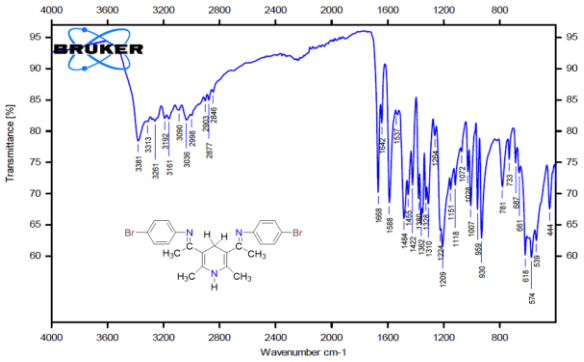


Figure 2: FT-IR of compound (M4)

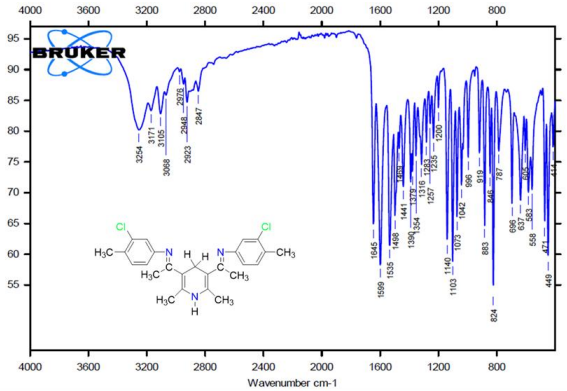


Figure 3: FT-IR of compound (M7)

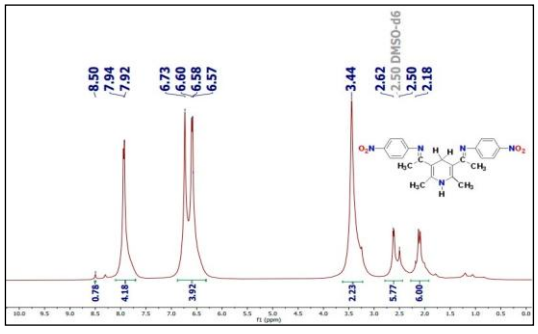


Figure 4: ^{1}H-NMR of compound (M2)

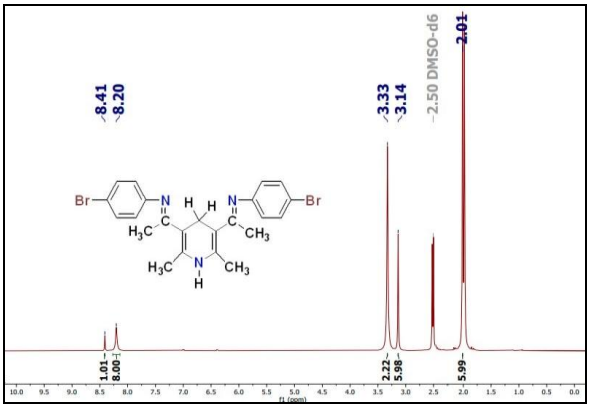


Figure 5: ^{1}H-NMR of compound (M4) .

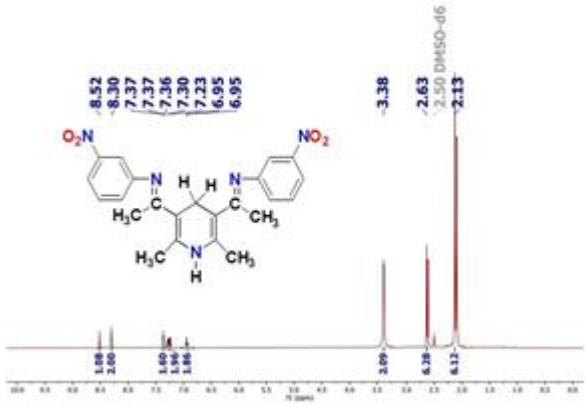


Figure 6: ^{1}H-NMR of compound (M5)

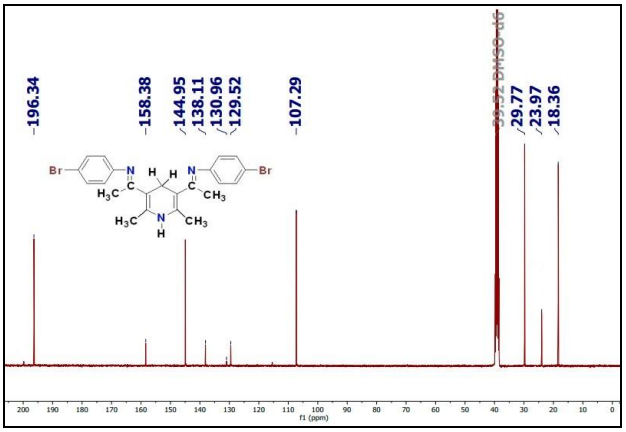


Figure 7: ^{13}C-NMR of compound (M4)

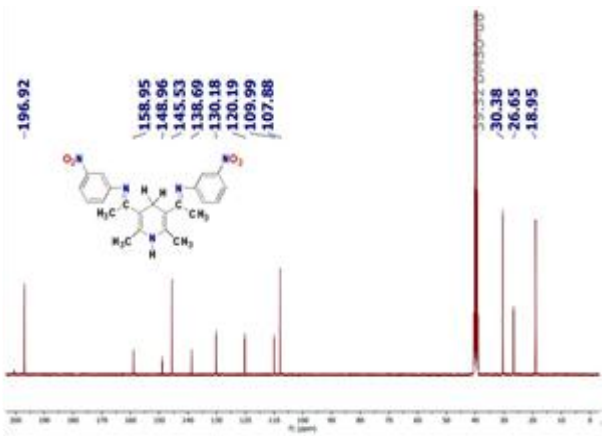


Figure 8: ^{13}C-NMR of compound (M5)

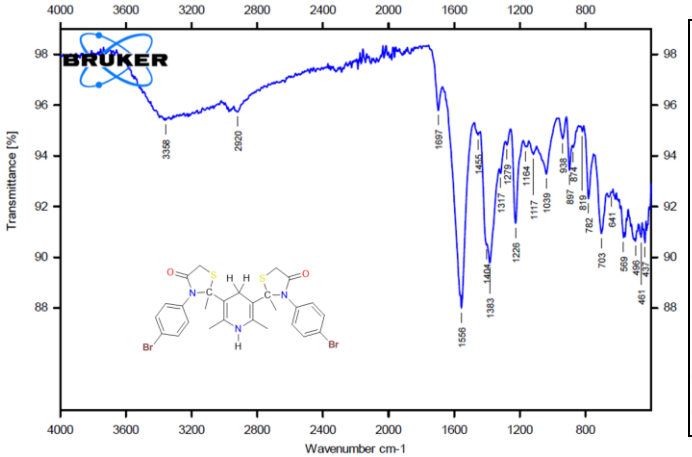


Figure 9: FT-IR of compound (A3)

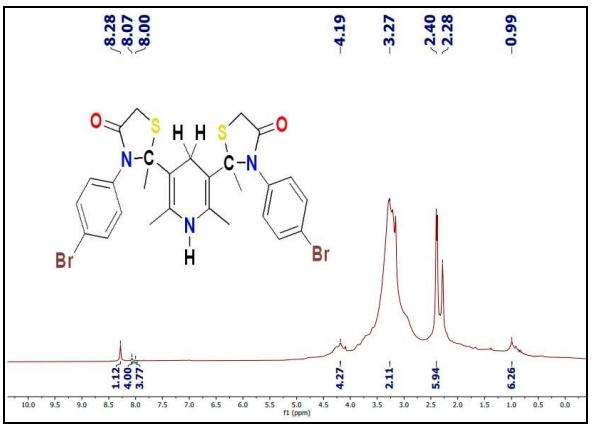


Figure 10: ^{1}H-NMR of the compound (A3)

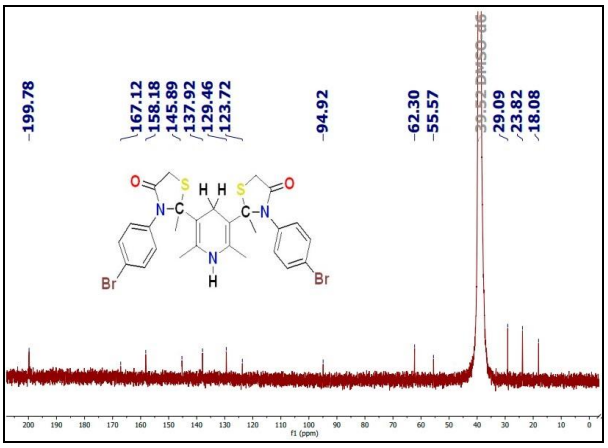


Figure 11: ^{13}C-NMR of the compound (A3)

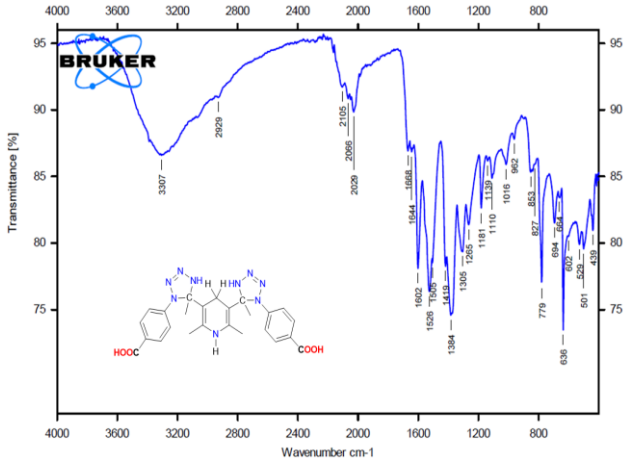


Figure 12: FT-IR of compound (A4)

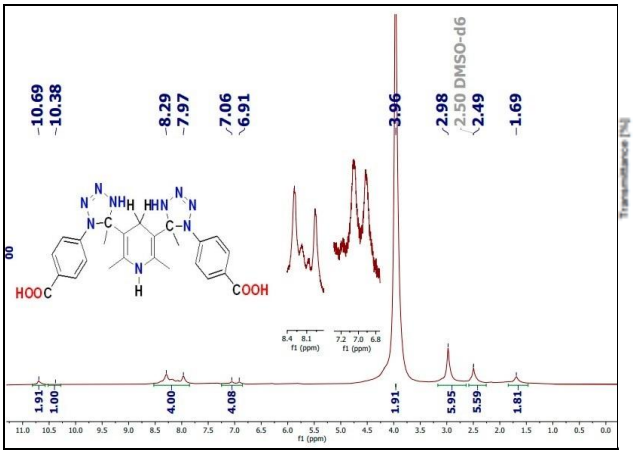


Figure 13: ^{1}H-NMR of the compound (A4)

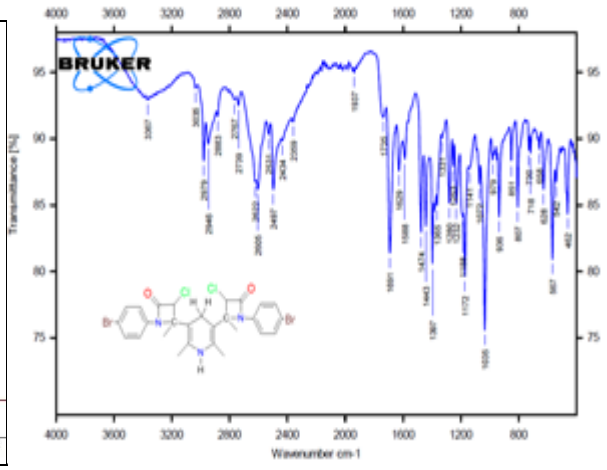


Figure 14: FT-IR of compound (A9)

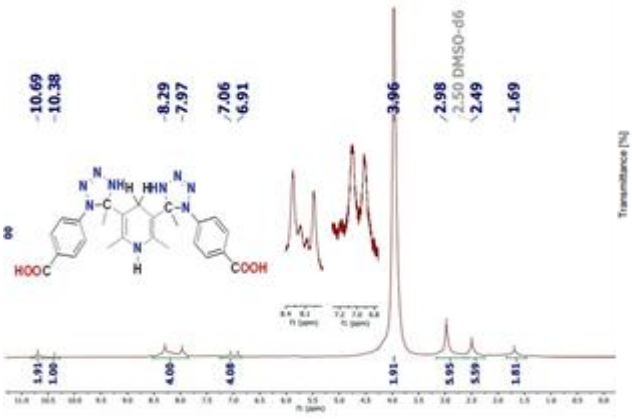


Figure 13: ^{1}H-NMR of the compound (A4)

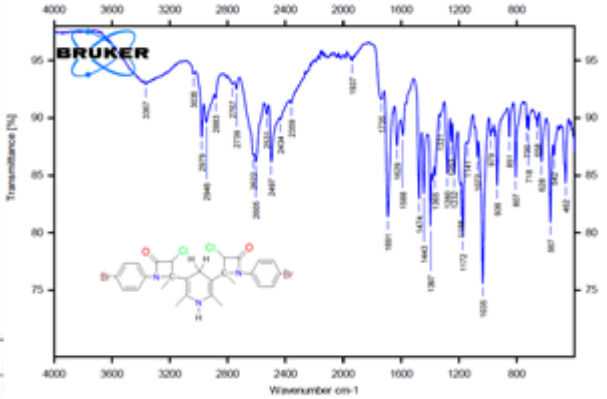


Figure 14: FT-IR of compound (A9)

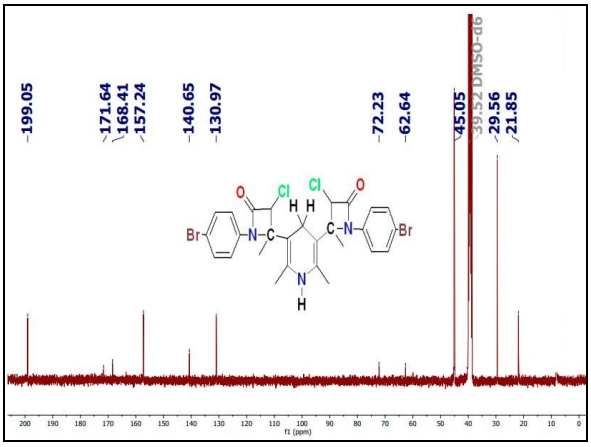


Figure 15: ^{1}H-NMR of the compound (A9)

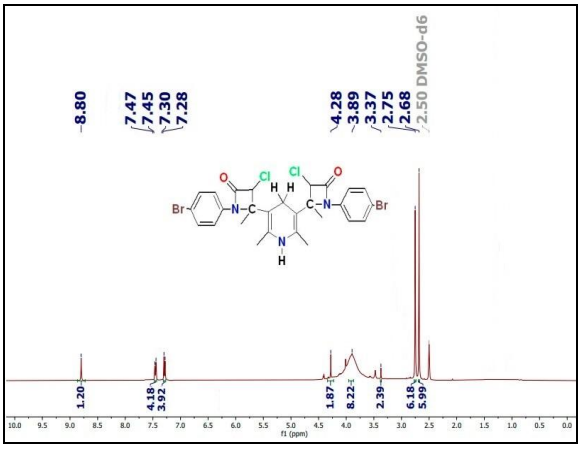


Figure 16: ^{13}C-NMR of the compound (A9)

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